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Review

Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox–Gastaut syndrome: A meta-analysis

Guido Lancman [a], Michael Virk [a], Huibo Shao [b], Madhu Mazumdar [b], Jeffrey P. Greenfield [a,d], Steven Weinstein [c,d], Theodore H. Schwartz [a,c,*]

[a] Department of Neurological Surgery, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
[b] Department of Public Health, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
[c] Department of Neurology and Neuroscience, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
[d] Department of Pediatrics, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA

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ABSTRACT

Purpose: Lennox–Gastaut syndrome (LGS) is an epileptogenic disorder that arises in childhood and is typically characterized by multiple seizure types, slow spike-and-wave complexes on EEG and cognitive impairment. If medical treatment fails, patients can proceed to one of two palliative surgeries, vagus nerve stimulation (VNS) or corpus callosotomy (CC). Their relative seizure control rates in LGS have not been well studied. The purpose of this paper is to compare seizure reduction rates between VNS and CC in LGS using meta-analyses of published data.

Methods: A systematic search of Pubmed, Ovidsp, and Cochrane was performed to find articles that met the following criteria: (1) prospective or retrospective study, (2) at least one patient diagnosed with Lennox–Gastaut syndrome, and (3) well-defined measure of seizure frequency reduction. Seizure reduction rates were divided into seizure subtypes, as well as total seizures, and categorized as 100%, >75%, and >50%. Patient groups were compared using chi-square tests for categorical variables and *t*-test for continuous measures. Pooled proportions with 95% confidence interval (95% CI) of seizure outcomes were estimated for total seizures and seizure subtypes using random effects methods.

Results: 17 VNS and 9 CC studies met the criteria for inclusion. CC had a significantly better outcome than VNS for >50% atonic seizure reduction (80.0% [67.0–90.0%] vs. 54.1% [32.1–75.4%], $p < 0.05$) and for >75% atonic seizure reduction (70.0% [48.05–87.0%] vs. 26.3% [5.8–54.7%], $p < 0.05$). All other seizure types, as well as total number of seizures, showed no statistically significant difference between VNS and CC.

Conclusions: CC may be more beneficial for LGS patients whose predominant disabling seizure type is atonic. For all other seizure types, VNS offers comparable rates to CC.

1. Introduction

Lennox–Gastaut syndrome (LGS) is an epileptogenic disorder arising in childhood with seizure control a therapeutic challenge.[1,2] Its characteristics can include multiple seizure types, slow spike-and-wave complexes on EEG and cognitive impairment.[3,4] LGS usually persists through adulthood and has a poor prognosis, despite extensive pharmacological treatment.[4,5] The most common seizure types include tonic, atonic, and atypical absence, but generalized tonic–clonic (GTC), myoclonic and complex partial seizures (CPS) can also be present.[2,6]

When medications fail and there is no resectable seizure focus, patients can proceed to one of two palliative surgeries, vagus nerve stimulation (VNS) or corpus callosotomy (CC). Although VNS was approved by the FDA in 1997 for treatment of refractory partial-onset seizures,[7] its efficacy for other seizure-types is recognized.[8] CC was first introduced as an experimental procedure in 1940[9] and has since been accepted in clinical practice to decrease the frequency and severity of generalized seizures, primarily atonic seizures,[10] although its efficacy in the treatment of other seizure types has also been recognized.[11]

VNS is usually recommended first because it is a reversible procedure and is thought to have seizure reduction rates comparable to those of CC but without the risks of a craniotomy.[1,12] However, no study has attempted to directly compare these rates with large samples of LGS patients. Furthermore, information on the two interventions' effectiveness for the different specific seizure types in LGS is widely scattered. We hypothesized that CC would prove more effective in reducing generalized epilepsy types, which include atonic, tonic, GTC, and myoclonic seizures.

* Corresponding author at: 525 E 68th St., Box 99, New York, NY 10065, USA. Tel.: +1 212 746 5620; fax: +1 212 746 8947.
E-mail addresses: schwarh@med.cornell.edu, gl10327@aol.com (T.H. Schwartz).

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2. Methods

2.1. Search strategy

Three authors (GL, MV, THS) independently performed a systematic search of PubMed, Ovidsp, and Cochrane for English-language studies published through December 2010. Search terms included all combinations of (1) Lennox–Gastaut syndrome, LGS, Lennox, and (2) VNS, vagal nerve stimulation, vagus nerve stimulation, callosotomy, corpus callosum, commisurotomy. The investigators identified potentially relevant articles by reviewing abstracts and then thoroughly reviewed references.

2.2. Selection of studies

Inclusion criteria for this meta-analysis consisted of the following: (1) prospective or retrospective study, (2) case reports or group study, (3) at least one patient diagnosed with Lennox–Gastaut syndrome, and (4) well-defined measure of seizure frequency reduction, either in numbers or ranges, after VNS or CC. Studies were excluded if seizure frequency data for LGS could not be extracted from the study population's data, which sometimes included other primarily generalized epilepsies. Three authors (GL, MV, THS) independently reviewed studies that met inclusion criteria to determine their suitability and quality and unanimously agreed upon the studies to be included in this meta-analysis.

2.3. Data collection

Data were collected on the following: first author, year of study, retrospective or prospective study, type of treatment, number of LGS patients in study, gender, age at surgery, age at epilepsy onset, duration of epilepsy, etiology, VNS parameters, whether VNS patients had previous CC, partial vs. full CC, time of follow-up, complications, and seizure reduction rates for each seizure subtype and all seizures combined ("total seizures"), categorized as 100%, >75%, >50%, and <50%. In studies where patients were listed individually, means and sum totals were used to represent the study in the final analysis. Duplicate data between different studies were identified and excluded from the analyses. The corresponding author of the You et al. paper[13] was directly contacted regarding the CC complications in his paper, which he stated were all transient. If there were multiple follow-up points in a study with declining numbers of patients, and the data could not be extracted individually, then the latest follow-up point which maintained a large proportion of the initial sample was used, as agreed upon by the authors. Not all data were available in every study.

2.4. Statistical analysis

Characteristics of patients groups (VNS vs. CC) were compared using chi-square tests for categorical variables and *t*-test for continuous measures. *p* values less than 0.05 were considered significant. Pooled proportions with 95% confidence interval (95% CI) of seizure outcomes were estimated for total seizures and seizure subtypes by VNS and CC. To account for heterogeneity across studies, random effects models were used for the estimation. The differences between two pooled proportions were tested by evaluating the overlap of the 95% CI. The formula in the Wolfe and Hanley paper was followed to decide significance.[14] Publication bias was tested with Begg–Mazumdar bias indicator. Analyses were conducted in StatsDirect version 2.7.8 and STATA version 11. This study was approved by the Institutional Review Board of the New York Presbyterian-Weill Cornell Medical Center.

3. Results

3.1. Eligible articles

The literature search yielded 37 VNS and 23 CC abstracts, of which 13 VNS and 8 CC papers were excluded because they were review articles, lacked original data, or did not address seizure frequency (Fig. 1). After careful review and consideration of the remaining full text articles, 17 VNS studies[13,15–30] and 9 CC studies[13,31–38] were included. One study contained data on both VNS and CC patients independently.[13] Additionally, one CC study was split into groups for the analysis based upon data presentation.[34] All studies were published between 1990 and 2010, of which 14 were prospective and 12 were retrospective, resulting in a total of 203 VNS patients and 145 CC patients.

3.2. Group comparisons

VNS patients did not differ significantly from CC patients with respect to gender, mean age at epilepsy surgery, mean age of

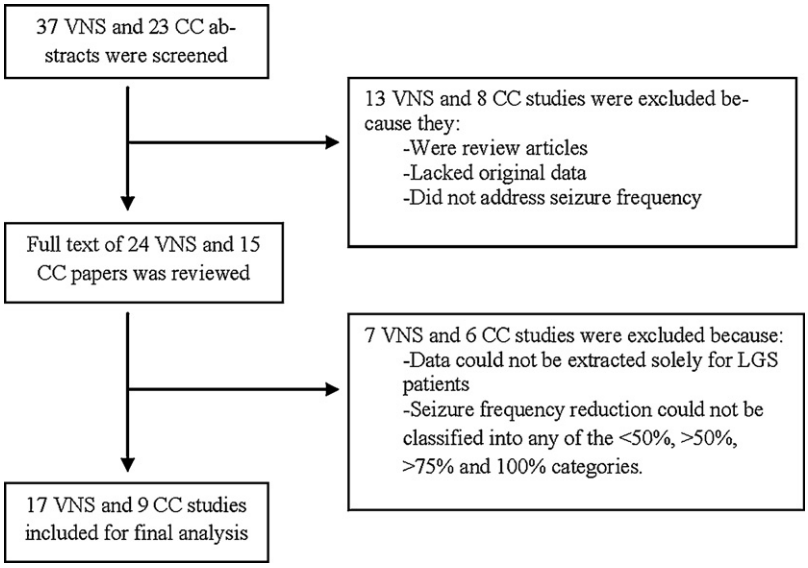

Fig. 1. Flow chart of study selection.